UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

MEMORANDUM

Date: May 31, 2012

SUBJECT: Tefluthrin: Dermal Penetration Study in Rats and *In Vitro* Dermal Penetration Studies in Rats and Humans

PC Code: 128912
Decision No.: 417629
Petition No.: NA
Risk Assessment Type: NA
TXR No.: 0055257
MRID No.: 47813014, 47813015, 47813016

DP Barcode: D368836
Registration No.: 100-RGAR
Regulatory Action: Section 3 Registration
Case No.: NA
CAS No.: 79538-32-2
40 CFR: NA

Ver.Apr.08

FROM: Charles Smith, Senior Environmental Scientist/Risk Assessor 5/31/12
Risk Assessment Branch VI
Health Effects Division (7509P)

THROUGH: Felecia Fort, Chief
Risk Assessment Branch VI
Health Effects Division

TO: BeWanda Alexander/Richard Gebken, Risk Management Team 10
Insecticide Branch
Registration Division (7505P)
Risk Management Division

I. CONCLUSIONS

These studies are **acceptable**. The *in vivo* dermal penetration study is a **guideline** study and satisfies the guideline requirements (OPPTS 870.7600; OECD 427) for a dermal penetration study in rats; the *in vitro* studies are **non-guideline** and provide additional information comparing the dermal penetration of the test compound in human and rat skin.

At 24 hours, dermal absorption for the *in vivo* study was 0.79% (*stratum corneum* + application site skin + absorbed); dermal absorption for the *in vitro* rat skin was 0.9%; and dermal absorption for the *in vitro* human skin was below the level of quantitation. It was concluded that although

human epidermis exhibits significant resistance to dermal penetration that the 24 hour dermal absorption value from the rat *in vivo* study of 0.79% should be used in tefluthrin risk assessment.

II. ACTION REQUESTED

The Registration Division (RD) requested that the Health Effects Division (HED) review the rat *in vivo* dermal penetration study (MRID 47813014), the rat *in vitro* dermal penetration study (MRID 47813015), and the human *in vitro* dermal penetration study (MRID 47813016) submitted by the registrant to estimate dermal penetration of tefluthrin. These studies were performed using a microencapsulated suspension formulation so as to be representative of the multiple microencapsulated suspension products registered for tefluthrin.

III. BACKGROUND

In 1997, HED determined that a dermal absorption factor of 25% should be used for tefluthrin (Rowland and Swentzel; TXR 0013631; 7/29/1997). This dermal absorption factor was based on the weight-of-the-evidence available for structurally-related pyrethroids. As part of the request for a Section 3 registration for tefluthrin on sugar beet seed, Syngenta submitted a dermal penetration triple pack with the intent of using the parallelogram approach to estimate tefluthrin dermal absorption. The basic concept is that if the *in vivo* human and rat dermal absorption data is generated under the same conditions as the *in vitro* human and rat skin data, the ratio of dermal absorption factors (human skin/rat skin) measured *in vitro* will be the same as the ratio of dermal absorption factors (human/rat) measured *in vivo*.

IV. RESULTS/DISCUSSION

HED has reviewed the submitted studies and they have been considered acceptable. The *in vivo* dermal penetration study is a **guideline** study and satisfies the guideline requirements (OPPTS 870.7600; OECD 427) for a dermal penetration study in rats; the *in vitro* studies are **non-guideline** and provide additional information comparing the dermal penetration of the test compound in human and rat skin.

1. *In vivo* studies in rats

In the *in vivo* dermal penetration study (MRID 47813014), [^{14}C]-tefluthrin (≥92.2% radiochemical purity, Batch 83-19) in a microencapsulated suspension formulation containing 200 g/L tefluthrin was applied in a single dose to 16 male Wistar (Alpk:AP$_f$SD) rats on 10 cm^2 skin areas (two areas of 5 cm^2) at a dose level of 10 mg/rat (1 mg/cm^2). Four time points were studied including 6, 24, 72, and 120 hours post-dosing. The *in vivo* absorption of tefluthrin was relatively consistent after 24 (0.79%) or 120 (1.1%) hours (assuming dermal absorption is equivalent to *stratum corneum* + application site skin + absorbed).

2. *In vitro* study in rat skin

In the *in vitro* rat dermal penetration study, [^{14}C]-tefluthrin (≥92.2% radiochemical purity, Batch 83-19) in a microencapsulated suspension formulation containing 200 g/L tefluthrin was applied

in a single dose to excised rat membranes (MRID 47813015) at a nominal dose level of 2.54 mg/membrane (1 mg/cm^2). Four time points were studied including 6, 8, 10, and 24 hours post-dosing. The *in vivo* absorption of tefluthrin was linear across the study and resulted in 0.90% absorbed after 24 hours.

3. *In vitro* study in human skin

In the *in vitro* human dermal penetration study, [^{14}C]-tefluthrin (≥92.2% radiochemical purity, Batch 83-19) in a microencapsulated suspension formulation containing 200 g/L tefluthrin was applied in a single dose to human epidermal membranes (MRID 47813016) at a nominal dose level of 2.54 mg/membrane (1 mg/cm^2). Four time points were studied including 6, 8, 10, and 24 hours post-dosing. The *in vivo* absorption of tefluthrin was close to, or below, the limit of quantitation (LOQ = 0.01 µg/cm^2/hr) throughout the entire 24 hour study period. As a result, a rate of absorption could not be calculated.

4. Tefluthrin dermal penetration value for use in risk assessment

Since a human *in vitro* rate of absorption could not be calculated, the parallelogram approach could not be used to estimate a human dermal penetration factor. It was concluded that although human epidermis exhibits significant resistance to dermal penetration (i.e., absorption values below the LOQ) that the 24 hour dermal absorption value from the rat *in vivo* study of 0.79% should be used for tefluthrin risk assessment purposes.

DATA EVALUATION RECORD

TEFLUTHRIN

Study Types: OPPTS 870.7600 [§85-2]; Dermal Penetration Study in Rats
Non-Guideline; *In Vitro* Dermal Penetration Studies in Rats and Humans

Work Assignment No. 6-1-227 (MRIDs 47813014, 47813015, and 47813016)

Prepared for
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
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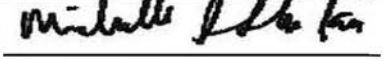
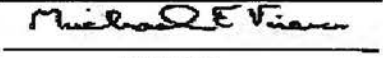
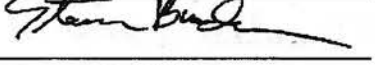
Primary Reviewer: Michael E. Viana, Ph.D., D.A.B.T.	Signature: Date:	 *10/01/09*
Secondary Reviewer: Michelle J. Sharpe-Kass, M.S.	Signature: Date:	 *10/01/09*
Program Manager: Michael E. Viana, Ph.D., D.A.B.T.	Signature: Date:	 *10/01/09*
Quality Assurance: Steven Brecher, Ph.D., D.A.B.T.	Signature: Date:	 *10/01/09*

Disclaimer

This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel

EPA Reviewer: Charles Smith
Risk Assessment Branch VI, HED (7509P)

Signature:
Date: 5/31/12

Template version 03/12

DATA EVALUATION RECORD

STUDY TYPES: *In Vivo* Dermal Penetration Study in Rats, OPPTS 870.7600 ['85-2], OECD 427; and *In Vitro* Dermal Penetration Studies in Rats and Humans, Non-Guideline.

PC CODE: 128912 **DP BARCODE:** D368836
TXR#: 0055257

TEST MATERIAL (RADIOCHEMICAL PURITY): Tefluthrin (≥92.2%)

SYNONYMS: (2,3,5,6-tetrafluoro-4-methylphenyl)methyl (1*R*,3*R*)-*rel*-3-[(1*Z*)-2-chloro-3,3,3-trifluoro-1-propenyl]-2,2-dimethylcyclopropanecarboxylate

CITATION: Silcock, R.C. (2002) Tefluthrin 20CS formulation – *in vivo* dermal absorption in the rat: final report. Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK. Laboratory Report No.: CTL/UR0696, October 29, 2002. MRID 47813014. Unpublished

Davies, D.J. (2002) Tefluthrin 20CS formulation – *in vitro* absorption of tefluthrin through rat epidermis: final report. Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK. Laboratory Report No.: CTL/JV1693, June 6, 2002. MRID 47813015. Unpublished

Davies, D.J. (2002) Tefluthrin 20CS formulation – *in vitro* absorption of tefluthrin through human epidermis: final report. Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK. Laboratory Report No.: CTL/JV1694, June 6, 2002. MRID 47813016. Unpublished

SPONSOR: Syngenta Crop Protection, Inc., 410 Swing Road, P.O. Box 18300, Greensboro, NC

EXECUTIVE SUMMARY: In an *in vivo* dermal penetration study (MRID 47813014), [^{14}C]-tefluthrin (≥92.2% radiochemical purity, Batch 83-19) in a microencapsulated suspension formulation containing 200 g/L tefluthrin was applied in a single dose to 16 male Wistar (Alpk:AP$_f$SD) rats on 10 cm^2 skin areas (two areas of 5 cm^2) at a dose level of 10 mg/rat (1 mg/cm^2). The dosing areas were covered and animals were exposed for six hours, at which time the application sites of all rats were washed. Urine, feces, and cage washes were collected at 6, 24, 48, 72, 96, and 120 hours post-dosing. Four animals/time point were killed at 6, 24, 72 and 120 h after the material was first applied to the skin. At the end of the exposure period, the cover was removed, the skin was washed and urine, feces, cage wash, blood, residual carcass, treated

and surrounding skin and the protective dressing were collected and analyzed for radioactivity.

In two accompanying *in vitro* dermal penetration studies, [^{14}C]-tefluthrin (≥92.2% radiochemical purity, Batch 83-19) in a microencapsulated suspension formulation containing 200 g/L tefluthrin was applied in a single dose to either excised rat (MRID 47813015) or human epidermal (MRID 47813016) membranes at a nominal dose level of 2.54 mg/membrane (1 mg/cm^2). Epidermal membranes were maintained in glass diffusion cells at approximately 32°C. The integrity of the membranes was first tested by measurement of their electrical resistance. Then the formulation was applied at a rate of 5 µL/cm^2 to 4-6 membranes. Groups of cells were assigned to each of two exposure periods, 6 or 24 hours. For cells assigned to the 24 hour exposure period, receptor fluid samples were collected at 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, and 24 hours. For cells assigned to the 6 hour exposure period, receptor fluid samples were taken at 6 hours only. At the end of the exposure period, the exposed surfaces of the epidermal membranes were decontaminated by swabbing the application site with natural sponges pre-wetted with 3% Teepol® and with additional sponges pre-wetted with water. The human epidermal preparations were also tape-stripped to remove the *stratum corneum*. The amounts of radioactivity in the various samples were determined by liquid scintillation counting.

In the *in vivo* study, recovery was quantitative, ranging from 105.5-108.4% of the applied dose (AD). Almost all of the radioactivity was recovered in the skin wash 6 hours after application (101.9-104.6% AD). A small amount (≤0.4% AD) was removed by the terminal skin wash at 24, 72, and 120 hours post-application; this amount decreased with increasing time. Residues on the O-rings, charcoal covers, and elastic bandages accounted for ≤1.6% AD. The total unabsorbed dose ranged from 105.0-107.4% AD.

In the rats terminated at 6 hours post-application, the radioactivity present in the skin beneath the application site amounted to 0.6% AD, with 0.4% AD present in the *stratum corneum*. Over this exposure period, 0.2% AD was absorbed. After 24 hours, the residues present in the skin had declined to 0.3% AD, with 0.1% AD present in the *stratum corneum*. Residue levels in the skin continued to decline with time, falling to less than 0.1% AD at 120 hours post-dosing. The amount of the dose absorbed slowly increased with time, reaching 0.5% AD at 24 hours, 0.8% AD at 72 hours, and 1.0% AD at 120 hours. Most of the absorbed dose was excreted after 120 hours, with 0.3% AD found in urine and 0.5% AD present in the feces. It was stated that approximately half of the absorbed dose was eliminated in the bile for excretion in the feces and approximately 25% of the absorbed dose was excreted in the urine. The most appropriate value for risk assessment is a dermal absorption of 0.79% (*stratum corneum* + application site skin + absorbed), observed at 24 hours after application.

In rat epidermal membranes exposed *in vitro* for 6 hours (representing a typical work day), the absorption of the test compound was 1.58 µg/cm^2, equivalent to 0.16% AD. In rat epidermal membranes exposed for 24 hours, absorption of the test compound was essentially linear over the exposure period. The rate of absorption was determined to be 0.37 µg/cm^2/h. During the 24 hour time course, the amounts of the test compound absorbed over periods representing typical working day lengths (6-10 hours) were 1.68-3.18 µg/cm^2. Absorption increased to 8.69 µg/cm^2 at 24 hours, which represented 0.90 % AD. Recovery was quantitative, with 102% AD accounted for at both 6 and 24 hours. Almost all of the radioactivity was recovered in the skin

wash (95.9-99.7% AD). A small amount of radioactivity was associated with the epidermal membrane, and the amount declined with time.

In human epidermal membranes exposed *in vitro* for 6 hours (representing a typical work day), the absorption of the test compound was 0.53 $\mu g/cm^2$, equivalent to 0.06% AD. In human epidermal membranes exposed for 24 hours, absorption of the test compound was close to or below the limit of quantitation (0.33 $\mu g/cm^2$). The rate of absorption was not determined. Recovery was quantitative, with 100-106% AD accounted for at 6 and 24 hours. Almost all of the radioactivity was recovered in the skin wash (99.9-106% AD). A small amount of radioactivity was associated with the *stratum corneum*, and the amount was unchanged with time. A very small amount of radioactivity was associated with the epidermal membrane, the level again was unchanged with time.

The reviewers conclude that the *in vitro* dermal penetration of the test compound through both human and rat epidermis is very low, with human epidermis exhibiting greater resistance to dermal penetration than rat epidermis.

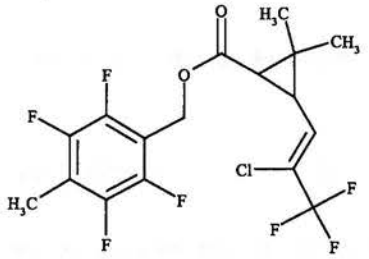
These studies are **acceptable**. The *in vivo* dermal penetration study is a **guideline** study and satisfies the guideline requirements (OPPTS 870.7600; OECD 427) for a dermal penetration study in rats; the *in vitro* studies are **non-guideline** and provide additional information comparing the dermal penetration of the test compound in human and rat skin.

COMPLIANCE: Signed and dated Data Confidentiality, GLP Compliance, and Quality Assurance statements were provided. It was stated that the studies were performed in compliance with the UK Principles of Good Laboratory Practice (1999, Statutory Instrument No. 3106), and that these principles are in accordance with the OECD Principles of Good Laboratory Practice, revised 1997 (ENV/MC/CHEM(98)17).

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material

Radiolabeled test material	[^{14}C]-Tefluthrin
Radiochemical purity	≥92.2% (HPLC)
Specific activity	20.7 MBq/mmol
Batch reference	83-19
Description	Suspension of microcapsules
Structure	

Location of the radiolabel not provided

Non-radiolabeled test material	Tefluthrin
Description	White solid
Batch reference	ASJ10025-02
Purity	99.3%
CAS # for TGAI	79538-32-2

2. Relevance of test material to proposed formulation(s):

The radiolabeled test material was incorporated into a microencapsulated suspension containing 200 g/L of tefluthrin (20CS formulation concentrate).

3. Test animals

Species:	Rat (males only)	
Strain:	Wistar-derived (Alpk:AP$_f$SD)	
Age/weight at study initiation:	Age not specified; 201-238 g	
Source:	Biological Services Section, Alderley Park, Macclesfield, Cheshire, UK	
Housing:	Individually in stainless steel metabolism cages	
Diet:	Rat and Mouse No. 1 maintenance diet (Special Diets Services, Stepfield, Witham, Exxex, UK), *ad libitum*	
Water:	Tap water, *ad libitum*	
Environmental conditions:	**Temperature:**	22 ± 3EC
	Humidity:	30-70%
	Air changes:	At least 15/hr
	Photoperiod:	12 hr light/12 hr dark
Acclimation period:	At least 4 days	

B. STUDY DESIGN – *IN VIVO* STUDY

1. Dose

Rationale: It was stated that preliminary investigations were conducted to determine an appropriate dose volume and that this volume did not cause any skin irritation. Further, the

doses and exposure intervals were selected to represent typical exposures to the selected formulation concentrate.
Nominal doses: A nominal dose of 10 mg/rat (dose rate of 1 mg/cm^2) was used.

Actual doses: The mean achieved dose was 9.66 mg/rat.

Dose volume: 5 µL/cm^2

Duration of exposure (time from dose to skin wash): 6 hours

Termination period (time from dose to terminal sacrifice): 6, 24, 72, and 120 hours post-application

Number of animals/time point: 4 male rats/time point

2. **Animal preparation:** On the day before dosing, the fur behind both shoulders of each rat was shaved, and the exposed skin was swabbed with acetone. Two plastic O-rings (25.25 mm internal diameter) with screw thread caps were attached to the skin (behind each shoulder) with cyanoacrylate glue. A strip of non-occlusive elastic bandage was wrapped around the rat and over the rings to help secure them in place. Each of the two sites had an area of 5.0 cm^2, for a total application area of 10 cm^2.

3. **Dose preparation, administration and quantification**

Preparation: It was stated that the formulation concentrate was used directly as supplied by the Sponsor. The formulation concentrate consisted of non-labeled and radiolabeled test substance homogeneously dispersed in the formulation by the Sponsor. The dosing solution was stirred continuously throughout dosing. Homogeneity of the dose formulation was analyzed via liquid scintillation counting (LSC).

Application: Each rat was weighed. The elastic bandage was removed and discarded. The screw cap was removed from each site, and 25 µL of the test formulation was applied to the skin surface using a positive displacement pipette, to yield 5 µL/cm^2 and 50 µL per rat. Following application, the edge of the pipette tip was used to spread the dispensed dose over the defined area; separate tips were used for each application site. The application sites were protected by charcoal filter covers held in place by the screw caps. A new elastic bandage was wrapped around the rat and over the O-rings to help hold them in place.

Quantification: The radiochemical purity of the test substance was determined by TLC both prior to dosing and immediately following dosing to confirm the stability of the radiolabeled test compound in the formulation concentrate. The homogeneity and specific activity of the dose formulations were determined by LSC.

4. **Skin wash:** Six hours after dosing, the application sites of all rats were washed. Each rat was held above a tray to enable the collection of any excreta, and the elastic bandage was removed and retained for analysis. The screw caps and charcoal covers were removed and

retained separately for analysis. Each application site was washed using a minimum of six pieces of natural sponge pre-wetted with a 3% aqueous solution of Liquid Dove soap, followed by six pieces of sponge wetted with water. Two dry sponges were used to dry the skin. All of the sponges used for a rat were retained in a single container for analysis. The application sites were protected with screw caps fitted with nylon gauze covers, and new elastic bandages were wrapped around the rats and over the rings for the remainder of the experiment.

5. **Excreta collection:** Urine and feces were collected separately into receivers cooled with dry ice at 6, 24, 48, 72, 96, and 120 hours post-dosing. With the exception of the terminal collection, each cage was washed with water immediately after urine collection. Any urine or feces collected on the tray during the skin wash was added to the corresponding 6 hour excreta collection. Excreta were stored frozen (-20°C) and cage washes were refrigerated prior to analysis.

6. **Study termination and sample collection:** Groups of four rats were euthanized at 6, 24, 72, and 120 hours post dosing. Each rat was lightly anesthetized with Halothane Ph Eur vapor, and the elastic bandage removed and added to the same container as previous bandages for each rat, as appropriate. The screw caps and covers (charcoal or nylon gauze) were removed and retained. The skin sites were washed as previously described, and the rats were then killed by exsanguination. The skin beneath each application site together with an annular ring of skin around each site was excised. The O-rings were detached and retained with the screw caps for analysis, and the skin beneath the rings was washed and dried with additional sponges that were retained with the other sponges used for each rat. The application sites were then tape-stripped to remove the *stratum corneum*, and the residual skin and tape strips were retained separately. Any urine present in the bladder was collected and added to the appropriate sample. The gastrointestinal tract (including contents) was removed and retained for analysis; the residual carcass was retained separately. Each cage was then washed with ethanol:water (1:1, v/v), and this final wash was retained for analysis. Samples were stored frozen, with the exception of whole blood and final cage washes which were stored refrigerated.

7. **Sample preparation and analysis:** Details of sample preparation are provided in Table 1. The amounts of radioactivity in the various samples were determined by LSC. Replicate samples were counted to a 0.5% standard deviation or for a maximum of 10 minutes each in an appropriate scintillation cocktail. The results were corrected for background activity and counting efficiency (external standard used), and disintegrations per minute were calculated using the appropriate quench correction data entered into the counter's computer. The limit of detection was taken to be twice the background values for blank samples in appropriate scintillation cocktails. It was stated that combustion efficiencies of the sample oxidizer were determined at regular intervals during each series of oxidations. Total amounts of radioactivity in samples were reported as percentage of the applied dose.

TABLE 1. Sample preparation details [a]	
Sample media	**Preparation details**
Urine, cage wash, plasma	Direct LSC
Feces	Mixed with water to a homogeneous paste and oxidized
Pipette tips, O-rings, charcoal and gauze covers, and elastic bandages	Extracted with ethanol
Sponges, tape strips, skin, and residual carcasses	Solubilized in Soluene tissue digestant
Whole blood	Oxidized
Gastrointestinal tract and contents	Homogenized and oxidized

a Information was obtained from page 21 of MRID 47813014.

C. STUDY DESIGN – *IN VITRO* STUDIES

1. Dose

Rationale: In the *in vitro* studies (MRIDs 47813015 and 47813016), it was stated that the application rates and exposure conditions used represent predicted exposure conditions and were requested by the Sponsor.

Nominal doses: A nominal dose of 2.54 mg was used. A dose rate of 1 mg/cm^2 was used in all studies.

Actual doses: The mean applied dose was 2.45 mg/cell.

Dose volume: 5 µL/cm^2 in all studies

Duration of exposure (time from dose to skin wash): 6 or 24 hours

Receptor fluid sampling (24 h exposures): 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, and 24 hours

Number of membranes/time point: 4-6 intact membranes from at least two subjects

2. Skin preparation (*in vitro* studies)

a. **Rat skin:** Skin from male Wistar-derived rats (Charles River UK Ltd., Margate, Kent, UK) was used. Fur from the dorsal and flank regions was carefully shaved; the clipped area was excised and any subcutaneous fat removed (method of euthanasia not provided). The skins were soaked for approximately 20 hours in 1.5 M sodium bromide and then rinsed in distilled water. The epidermis was then carefully peeled from the dermis and stored frozen on aluminum foil until use.

b. **Human skin:** Human whole skin samples were obtained *post mortem* (source not provided). Extraneous tissue was removed, and the skin samples were immersed in 60°C water for 40-45 seconds. The epidermis was then teased away from the dermis and stored frozen on aluminum foil until use.

3. **Diffusion cell design and receptor fluid:** A glass diffusion cell was used to study the dermal penetration of the test substance; a drawing of a diffusion cell is included as an Appendix at the end of this DER. Each cell consisted of a donor chamber and a receptor chamber between which the epidermal membrane was positioned on a support grid. The cells were unoccluded but had a non-occlusive carbon filter applied to the top of the donor chamber to capture any volatile components of the dose formulation. The receptor fluid was 50% ethanol in distilled water. The receptor chamber was warmed by a water bath maintained at 32 ± 1°C. The volume of fluid in the receptor chamber was maintained by replacement of an equal volume following sampling.

4. **Membrane integrity and membrane selection:** The integrity of the epidermal membranes was determined by measurement of their electrical resistance across the membrane. Rat membranes with a measured resistance of <2.5 kΩ were regarded as having a lower integrity than normal; human membranes with a measured resistance of <10 kΩ were regarded as having a lower integrity than normal. These membranes were discarded without use.

5. **Dose preparation, administration and quantification**

   Preparation: Same as above (*in vivo* study)

   Application: A pretreatment sample was taken from each receptor chamber for LSC analysis, and an equal volume of receptor fluid was added to replace the volume removed. Groups of cells were assigned to each of two exposure periods (6 or 24 hours), and 12.7 µL of the test compound was applied. The cells were unoccluded, but had a non-occlusive carbon filter applied.

   Quantification: Same as above.

6. **Mass balance:** The non-occlusive covers were removed, and then the donor chambers were removed; both the covers and chambers were washed with ethanol. The epidermal surface of the membrane was gently swabbed with natural sponges pre-wetted with 3% Teepol®, followed by sponges wetted with water. The sponges were digested with Soluene 350® for analysis. The remaining epidermis was removed and digested with Soluene 350®. The receptor chamber and support grids were soaked in ethanol. Samples of all washes, digests, and soaking solutions were taken for LSC analysis; the whole digest of the epidermal membrane was analyzed by LSC.

II. RESULTS

A. *IN-VIVO* STUDY: Results of the *in-vivo* dermal penetration study are presented in Table 2. Recovery was quantitative, ranging from 105.5-108.4% of the applied dose (AD). Almost all of the radioactivity was recovered in the skin wash 6 hours after application (101.9-104.6% AD). An additional 0.4% AD was removed by the terminal skin wash at 24 hours, declining to 0.2% at 72 hours and less than 0.1% at 120 hours post-application. Residues on the O-rings accounted for less than 0.3% AD, and it was stated that these were attributed to deposits made during skin washing. Residues on the charcoal covers accounted for ≤1.6% AD; residues on the elastic bandage accounted for less than 1.3% AD. The total unabsorbed dose ranged from 105.0-107.4% AD.

In the rats terminated at 6 hours post-application, the radioactivity present in the skin beneath the application site amounted to 0.6% AD, with 0.4% AD present in the *stratum corneum*. Over this exposure period, 0.2% AD was absorbed. After 24 hours, the residues present in the skin had declined to 0.3% AD, with 0.1% AD present in the *stratum corneum*. Residue levels in the skin continued to decline with time, falling to less than 0.1% AD at 120 hours post-dosing. The *in vivo* absorption of tefluthrin was relatively consistent after 24 (0.79%), 72 (1.0%), or 120 (1.1%) hours (assuming dermal absorption is equivalent to *stratum corneum* + application site skin + absorbed). Most of the absorbed dose was excreted after 120 hours, with 0.3% AD found in urine and 0.5% AD present in the feces. It was stated that approximately half of the absorbed dose was eliminated in the bile for excretion in the feces and approximately 25% of the absorbed dose was excreted in the urine.

TABLE 2. Mean (±SD) distribution of radioactivity (% administered dose) following the application of [^{14}C]-tefluthrin to skin.[a]

Sample	Exposure period			
	6 hours	24 hours	72 hours	120 hours
6 hour skin wash	NA	101.90±2.49	102.48±3.86	104.56±4.95
Terminal skin wash	103.51±6.27	0.42±0.01	0.18±0.17	0.05±0.06
Stratum corneum	0.42±0.22	0.13±0.03	0.07±0.06	0.03±0.01
Application site skin	0.19±0.05	0.20±<0.01	0.11±0.09	0.04±0.02
Bandage	0.42±0.26	0.87±0.06	1.21±0.24	1.21±0.48
Charcoal covers	1.37±0.35	1.31±0.02	1.60±0.59	1.41±0.30
O-rings	0.15±0.02	0.19±0.08	0.21±0.06	0.10±0.05
Total unabsorbed	**106.06±5.88**	**105.03±2.41**	**105.87±3.57**	**107.38±5.44**
Urine	<0.01	0.11±<0.01	0.24±0.08	0.26±0.06
Feces	<0.01	0.05±0.05	0.32±0.09	0.49±0.21
Cage wash	<0.02	0.03±0.01	0.05±0.01	0.08±<0.01
GI tract and contents	0.03±<0.01	0.11±0.01	0.06±0.04	0.04±0.01
Carcass	<0.16	<0.16	<0.18	<0.17
Total absorbed	**0.21±<0.01**	**0.46±0.06**	**0.84±0.18**	**1.03±0.26**
Total recovered	**106.27±5.88**	**105.49±2.46**	**106.71±3.39**	**108.41±5.46**

a Data (n=2-4) were obtained from page 29 of MRID 47813014.
NA Not applicable

B. ***IN-VITRO* RAT STUDY:** In rat epidermal membranes exposed for 6 hours (representing a typical work day), the absorption of the test compound was 1.58 $\mu g/cm^2$, equivalent to 0.16% AD. In rat epidermal membranes exposed for 24 hours, absorption of the test compound was essentially linear over the exposure period. The rate of absorption was determined to be 0.37 $\mu g/cm^2/h$. During the 24 hour time course, the amounts of the test compound absorbed over periods representing typical working day lengths were 1.68 $\mu g/cm^2$ over 6 hours, 2.42 $\mu g/cm^2$ over 8 hours, and 3.18 $\mu g/cm^2$ over 10 hours. Absorption increased to 8.69 $\mu g/cm^2$ at 24 hours, which represented 0.90 % AD.

Recovery was quantitative, with 102% AD accounted for at both 6 and 24 hours (Table 3). Almost all of the radioactivity was recovered in the skin wash (95.9-99.7% AD). A small amount of radioactivity was associated with the epidermal membrane, and the amount declined with time (5.28% AD at 6 hours; 1.06% AD at 24 hours).

TABLE 3. Mean (±SD) distribution of radioactivity (% administered dose) following the application of [^{14}C]-tefluthrin to rat epidermal membranes.[a]

Sample	Exposure period	
	6 hours	24 hours
Volatile components	0.07±0.01	0.28±0.07
Skin wash	95.9±1.37	99.7±0.86
Donor chamber	0.20±0.13	0.19±0.10
Epidermal membrane	5.28±0.57	1.06±0.21
Total absorbed	**0.16±0.02**	**0.90±0.07**
Total recovered	**102±0.90**	**102±0.70**

a Data (n=4-6) were obtained from page 23 of MRID 47813015.

C. ***IN-VITRO* HUMAN STUDY:** In human epidermal membranes exposed for 6 hours (representing a typical work day), the absorption of the test compound was 0.53 $\mu g/cm^2$, equivalent to 0.06% AD. In human epidermal membranes exposed for 24 hours, absorption of the test compound was close to or below the limit of quantitation (0.33 $\mu g/cm^2$). The rate of absorption was not determined.

Recovery was quantitative, with 100-106% AD accounted for at 6 and 24 hours (Table 4). Almost all of the radioactivity was recovered in the skin wash (99.9-106% AD). A small amount of radioactivity was associated with the *stratum corneum*, and the amount was unchanged with time (0.23% AD at 6 hours; 0.22% AD at 24 hours). A very small amount of radioactivity was associated with the epidermal membrane, the level again was unchanged with time (0.04% AD at 6 hours; 0.05% AD at 24 hours).

TABLE 4. Mean (±SD) distribution of radioactivity (% administered dose) following the application of [^{14}C]-tefluthrin to rat epidermal membranes.[a]

Sample	Exposure period	
	6 hours	24 hours
Volatile components	0.05±<0.01	0.20±0.01
Skin wash	99.9±0.81	106±0.84
Donor chamber	0.03±0.01	0.06±0.01
Stratum corneum	0.23±0.09	0.22±0.05
Epidermal membrane	0.04±0.01	0.05±0.01
Total absorbed	**0.06±0.01**	**0.03**
Total recovered	**100±0.79**	**106±0.91**

a Data (n=5-6) were obtained from page 23 of MRID 47813016.

III. DISCUSSION AND CONCLUSIONS

A. INVESTIGATORS CONCLUSIONS: Following a 6 hour exposure period, the *in vivo* dermal absorption of [^{14}C]-tefluthrin from a CS formulation concentrate accounted for 0.5% of the applied dose over 24 hours and 1.0% of the applied dose over 120 hours. Recovery of the applied dose from the skin surface was almost quantitative following skin washing with a soap solution and water. The results obtained in the *in vitro* studies demonstrate that the rate of absorption of tefluthrin from the 20CS formulation was minimal for rat epidermis and negligible for human epidermis. For both the 6 and 24 hour exposure periods, any test material remaining on the surface of the epidermis was readily removed by skin washing.

B. REVIEWER COMMENTS: In the *in vivo* study, recovery was quantitative, ranging from 105.5-108.4% of the applied dose (AD). Almost all of the radioactivity was recovered in the skin wash 6 hours after application (101.9-104.6% AD). An additional 0.4% AD was removed by the terminal skin wash at 24 hours, declining to 0.2% at 72 hours and less than 0.1% at 120 hours post-application. Residues on the O-rings accounted for less than 0.3% AD, and it was stated that these were attributed to deposits made during skin washing. Residues on the charcoal covers accounted for ≤1.6% AD; residues on the elastic bandage accounted for less than 1.3% AD. The total unabsorbed dose ranged from 105.0-107.4% AD.

In the rats terminated at 6 hours post-application, the radioactivity present in the skin beneath the application site amounted to 0.6% AD, with 0.4% AD present in the *stratum corneum*. Over this exposure period, 0.2% AD was absorbed. After 24 hours, the residues present in the skin had declined to 0.3% AD, with 0.1% AD present in the *stratum corneum*. Residue levels in the skin continued to decline with time, falling to less than 0.1% AD at 120 hours post-dosing. The amount of the dose absorbed slowly increased with time, reaching 0.5% AD at 24 hours, 0.8% AD at 72 hours, and 1.0% AD at 120 hours. Most of the absorbed dose was excreted after 120 hours, with 0.3% AD found in urine and 0.5% AD present in the feces. It was stated that approximately half of the absorbed dose was eliminated in the bile for excretion in the feces and approximately 25% of the absorbed dose was excreted in the urine. The most appropriate value for risk assessment is a dermal absorption of 0.79% (*stratum corneum* + application site skin + absorbed), observed at 24 hours after application.

In rat epidermal membranes exposed *in vitro* for 6 hours (representing a typical work day), the absorption of the test compound was 1.58 $\mu g/cm^2$, equivalent to 0.16% AD. In rat epidermal membranes exposed for 24 hours, absorption of the test compound was essentially linear over the exposure period. The rate of absorption was determined to be 0.37 $\mu g/cm^2/h$. During the 24 hour time course, the amounts of the test compound absorbed over periods representing typical working day lengths were 1.68 $\mu g/cm^2$ over 6 hours, 2.42 $\mu g/cm^2$ over 8 hours, and 3.18 $\mu g/cm^2$ over 10 hours. Absorption increased to 8.69 $\mu g/cm^2$ at 24 hours, which represented 0.90 % AD. Recovery was quantitative, with 102% AD accounted for at both 6 and 24 hours. Almost all of the radioactivity was recovered in the skin wash (95.9-99.7% AD). A small amount of radioactivity was associated with the epidermal membrane, and the amount declined with time (5.28% AD at 6 hours; 1.06% AD at 24 hours).

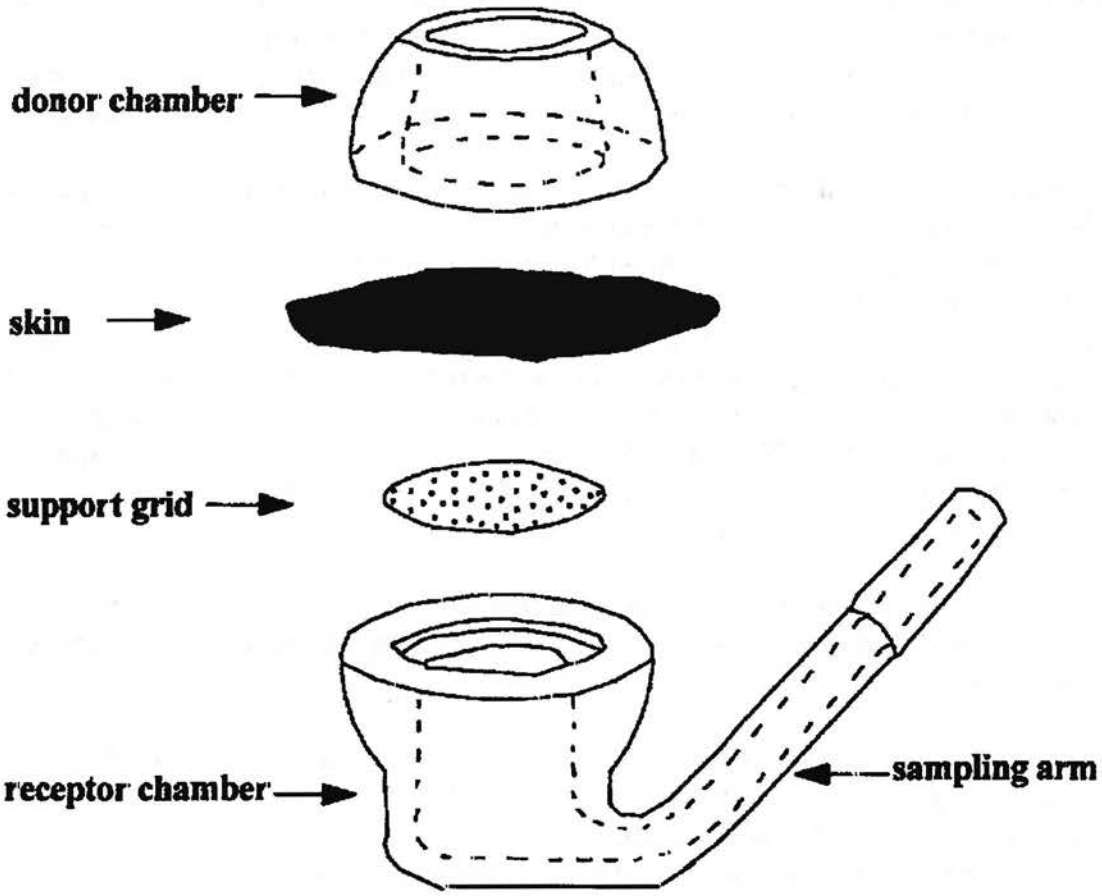
In human epidermal membranes exposed *in vitro* for 6 hours (representing a typical work day), the absorption of the test compound was 0.53 $\mu g/cm^2$, equivalent to 0.06% AD. In human epidermal membranes exposed for 24 hours, absorption of the test compound was close to or below the limit of quantitation (0.33 $\mu g/cm^2$). The rate of absorption was not determined. Recovery was quantitative, with 100-106% AD accounted for at 6 and 24 hours. Almost all of the radioactivity was recovered in the skin wash (99.9-106% AD). A small amount of radioactivity was associated with the *stratum corneum*, and the amount was unchanged with time (0.23% AD at 6 hours; 0.22% AD at 24 hours). A very small amount of radioactivity was associated with the epidermal membrane, the level again was unchanged with time (0.04% AD at 6 hours; 0.05% AD at 24 hours).

The reviewers conclude that the *in vitro* dermal penetration of the test compound through both human and rat epidermis is very low, with human epidermis exhibiting greater resistance to dermal penetration than rat epidermis.

These studies are **acceptable**. The *in vivo* dermal penetration study is a **guideline** study and satisfies the guideline requirements (OPPTS 870.7600; OECD 427) for a dermal penetration study in rats; the *in vitro* studies are **non-guideline** and provide additional information comparing the dermal penetration of the test compound in human and rat skin.

C. **STUDY DEFICIENCIES:** No deficiencies were noted.

APPENDIX


donor chamber
skin
support grid
receptor chamber
sampling arm